

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

CONTROLLED MORPHOLOGIES IN POLYMER DRUG FOR RELEASE OF DRUGS FROM POLYMER FILMS

BACKGROUND OF THE INVENTION

5 The present invention relates to a system for controlled drug release within a vessel lumen, and to a method and to a device for controlled drug release.

 A device for providing a continuous release of drugs over an extended period of time following from a single administration of a drug releasing material has wide application in treating disease. One type of continuous drug
10 release mechanism is based upon degradation of biodegradable polymers. The biodegradable polymers have drugs incorporated within them. As the biodegradable polymers hydrolyze over time, the drugs are released. Hydroxycarboxylic acid polymers have been used to release drugs in this manner.

 One other modality of drug release is a prolonged, though
15 discontinuous release of drugs. Frequently, with a discontinuous release, there is a lag phase of no or negligible drug release when a drug delivery device is delivered to an *in situ* site for drug release.

 One problem with sustaining drug release is that when drugs, particularly water soluble drugs, are incorporated into polymers, it is difficult to
20 prevent a rapid, uncontrolled release of the drugs. As used herein, the term "water soluble drug" is defined as a hydrophilic compound with a solubility in water greater than 1 percent (w/v) and that is practically insoluble in nonpolar organic solvents such as ethyl acetate, methylene chloride, chloroform, toluene, or hydrocarbons. This rapid, uncontrolled release from a drug-polymeric matrix is
25 known as a "burst effect." The burst effect is particularly troublesome with high drug loading.

 One other type of uncontrolled drug release is characterized by a "lag effect." The lag effect occurs when the rate of drug release decreases to a negligible value.

The degree of drug release from a polymeric-drug matrix is, in part, controlled by the morphology of the polymeric-drug matrix. The morphology is, for some embodiments, a single-phase dispersion and for other embodiments, is a multi-phase dispersion. A single-phase dispersion is typically transparent when viewed in
5 natural light. The single phase dispersion is clear and transparent because both the drug and the polymer have a mutual miscibility. A multi-phase dispersion has micro domains that give the dispersion a cloudy appearance. For some multi-phase dispersions, drugs are embedded in a polymeric matrix as particles.

Drug release is also controlled by the degree of drug loading.

10 Matrices that have dispersed drug particles that do not contact each other tend to have a slow release of drug. A drug carrier such as blood is typically required to move the drug through the matrix and into the bloodstream of a living being.

Drug-polymeric matrices have been used to deliver drugs *in situ* through a vehicle such as a stent. The drug-polymeric matrix has been applied as a
15 coating or a wrap to the stent. U.S. Patent No. 5,605,696, which issued February 25, 1997, describes a drug loaded polymeric material that is applied to an intravascular stent. The drug-polymeric matrix defines pores, multilayered to permit a combination of different drugs in a single stent. The stent also includes a rate controlling membrane that controlled retention and delivery of selected drugs to the
20 affected blood vessel. The drug is dispersed as small particles, having a maximum cross-sectional dimension of 10 microns.

DESCRIPTION OF THE DRAWINGS

Figure 1 is a perspective view of one embodiment of the drug
25 delivery system of the present invention wherein a system component is below the percolation threshold.

Figure 2 is a perspective view of one embodiment of the drug delivery system of the present invention wherein a system component is above the percolation threshold.

Figure 3a is a perspective view of the drug delivery system of the present invention wherein the pore structure is discontinuous.

Figure 3b is a perspective view of the drug delivery system of the present invention wherein the pore structure is semi- continuous.

5 Figure 3c is a perspective view of another embodiment of the drug delivery system of the present invention wherein the pore structure is continuous.

SUMMARY OF THE INVENTION

One embodiment of the present invention includes a drug release
10 system. The drug release system releases one or more drugs when implanted in a human being or other vertebrate but does not display a substantial release of drugs when outside of the human being or other vertebrates. The drug release system comprises a bulk polymer phase and a polymeric drug-enriched phase within the bulk polymer phase. The drug release system also includes at least one drug that is
15 incorporated in the polymeric drug-enriched phase. The drug release system of the present invention releases one or more drugs *in situ* while decreasing the rate of release of the drug when the device is not *in situ*. The drug profile release is predictable and preselectable.

Another embodiment of the present invention includes a coating that
20 comprises a drug release system. The drug release system has desirable film properties which render it useful as a coating for an implantable device. The present invention also includes an implantable device with a coating that is adhered to the implantable device. The coated implantable device releases one or more drugs in a predictable and preselectable manner when implanted in a human being or other
25 vertebrate.

Another embodiment of the present invention includes a method for substantially continuously releasing drugs. The method includes attaching or adhering a drug delivery system to an implantable medical device. The drug delivery system comprises a bulk polymer phase and a polymeric drug-enriched

phase within the bulk polymer phase. The drug release system also includes one or more drugs that are incorporated in the polymeric drug-enriched phase.

One other embodiment includes a device for continuously and predictably releasing drugs. The device comprises a drug release system that
5 comprises a bulk polymer phase. The drug release system also includes a drug-enriched polymeric phase within the bulk polymer phase. The drug release system also includes at least one drug which is incorporated into the polymeric drug-enriched phase wherein the drug-enriched phase comprises sites within the bulk polymer phase that are continuous in both cross-section and longitudinal directions.
10 Other embodiments of the device include implantable devices, such as a stent, catheter or guidewire, to which the drug release system is attached or adhered.

Another embodiment of the present invention includes a method for making a device for a continuous release of drugs. The method comprises providing a bulk phase polymer and providing a drug that is substantially insoluble in the bulk
15 phase polymer. The method also includes providing a drug enriched polymer. The drug enriched polymer is substantially insoluble in the bulk polymer. One or more of the drugs are soluble in the drug-enriched polymer. The method further comprises providing a solvent. The bulk phase polymer, the drug enriched polymer and the drug or drugs are blended in the solvent so that the drug or drugs are
20 incorporated into the drug receiving polymer and the drug enriched polymer is dispersed within the bulk polymer.

DETAILED DESCRIPTION

One embodiment of the present invention includes a drug release
25 system comprising two or more polymers that are insoluble in each other. The polymers are blended in a solvent to form two polymer phases which create a polymer blend. At least one drug is added to the polymer blend. The drug or drugs are soluble in one of the polymer phases, hereinafter referred to as the "drug-enriched polymer" or "drug enriched polymer phase." The polymer blend with the
30 drug enriched polymer phase is removed from the solvent and is allowed to set.

Once set, this drug release system has a morphology that has a predictable and preselectable drug release profile with desirable film properties. The desirable film properties include adherence or attachment to a polymeric or metal surface of an implantable device. Thus, the drug release system serves a dual function of
5 predictable, preselectable drug delivery and coating an implantable device.

The term "preselectable" as used herein refers to an ability to preselect one or more drugs to be released. "Preselectable," for some embodiments, also refers to a rate of drug release.

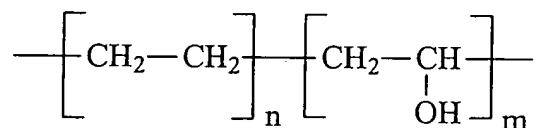
The polymer phase that includes the soluble drug, the drug-enriched
10 polymer phase, preferably has a glass transition temperature, T_g , less than human body temperature of about 37 degrees Centigrade. This polymer phase shall be referred to herein as a "drug-enriched polymer." Upon incorporating one or more drugs into the polymer, the polymer is kept at a temperature that is lower than the glass transition temperature. The term "glass transition temperature" as used herein
15 refers to a temperature at which the polymer chain undergoes long range motion characterized by a transition from a glassy state to a rubbery state. The glass transition temperature is also the temperature at which the rate of diffusion within the polymer phase changes by several orders of magnitude as the polymer goes from the glassy state to the rubbery state.

20 A polymer with a T_g that is less than 37 degrees Centigrade is used as the drug-enriched polymer because the diffusion rate of molecules, such as drug molecules within the polymer, decreases one to two orders of magnitude when the polymer is exposed to a temperature that is below the T_g . The T_g features of the drug enriched polymer impart to the polymer features that allow additional control
25 of the drug delivery rate. For instance, when the polymer is at a temperature below its T_g , it will not be within a living being, such as a human being. At these lower temperatures, the drug diffusion is suppressed and the drug does not prematurely diffuse through the bulk polymer. This is desirable because outside of a human being, drug diffusion through the polymer is problematic. Once the drug-enriched
30 polymer phase is implanted, the temperature of the polymer approaches its T_g and

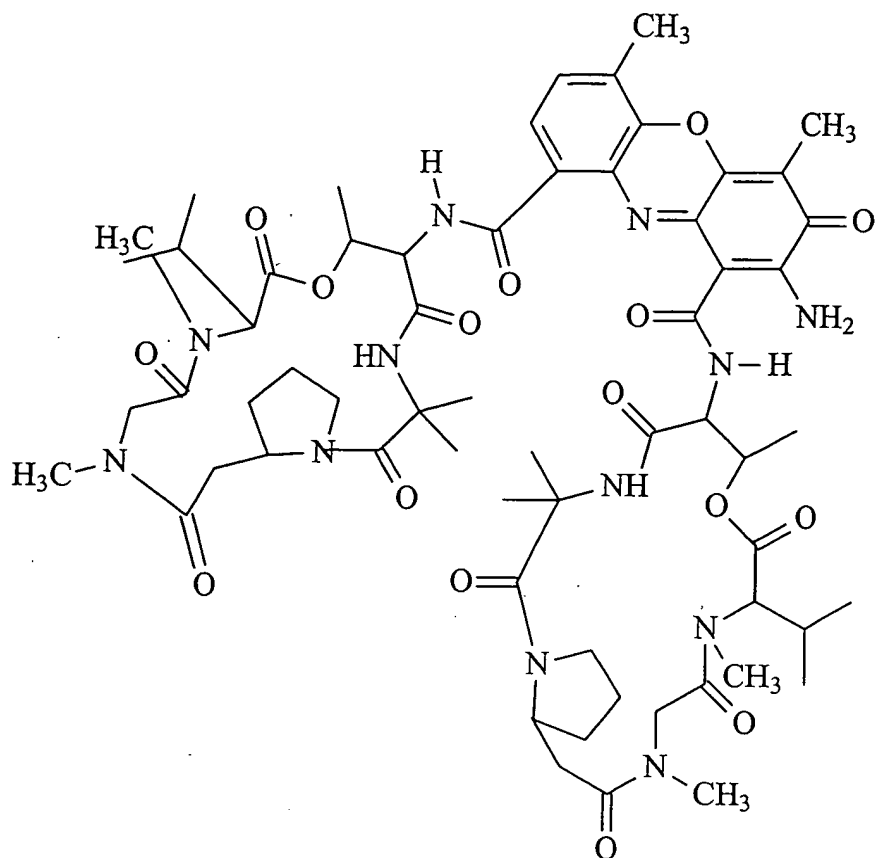
the rate of diffusion of drug through the polymer increases. The drug or drugs are deliverable to a predetermined site, such as to a lesion in a blood vessel. Once at this site, the drugs diffuse through the drug-enriched polymer. Polymers which can be used as the drug enriched phase include polyethylene oxide, PEO, and poly n-vinyl pyrrolidone.

The drug enriched polymer is at a concentration greater than the percolation threshold concentration, which is about 33-36%, assuming a morphology of spherical domains, to form a continuous drug enriched phase within the bulk polymer film. The term "percolation threshold" as is used herein refers to a state achieved when an aqueous drug enriched phase forms a continuous, interconnecting network throughout the bulk polymer thickness. The continuous drug enriched phase is one where the drug-enriched polymer phase is substantially uniformly distributed within the bulk phase, such as is shown generally, in one perspective view, at 10, in Figure 1.

The continuous drug-enriched polymer phase, is illustrated at 11 in Figure 1, for one embodiment. The bulk polymer 12 forming the phase which is not drug-enriched, referred to herein as the "bulk phase" or "bulk matrix" has acceptable film properties. One suitable polymer for use in the drug release system, as a bulk phase polymer, is poly(ethylene-co-vinyl) alcohol, which is also known as EVAL. EVAL is a thermoplastic polymer, manufactured by EVAL Company of America (EVALCA), of Lisle, Illinois. This polymer 12 has a formulation which is the following:



The drug- enriched polymer containing the drug has, for one embodiment, the formula:



One drug delivery system is composed of two components: one, a hydrophobic component, including but not limited to poly(ethylene-co-vinyl alcohol), and two, a hydrophilic component, which includes but is not limited to polyethylene glycol. The dissimilarity of solubility parameters of the components results in a phase separation of the two polymer phases. The two polymers are blended in a common solvent, such as dimethyl sulfoxide or N,N-dimethylacetamide, to form a solution. At least one therapeutic drug is added to the solution, such as the therapeutic drug, actinomycin D. However, the therapeutic drug or drugs are not limited to the antiproliferative class of drugs which has preferential solubility in the hydrophilic phase.

For some embodiments, the drug delivery system comprising the drug and polymer solution is applied to an implantable device to form a coating on the device. The coated device is dried to remove the solvent, by vacuum or by convection processing. The drying allows the polymers within the applied solution to form phases and to separate. Once dried, the coating retains flexibility.

If the volume percent of the drug enriched hydrophilic phase is less than about 30%, the hydrophilic polymer and drug will exhibit a discontinuous pore structure, as shown at 10 in Figure 1. The discontinuous pore structure shown in Figure 1 is defined as being below the percolation threshold.

If the volume percent of the drug enriched hydrophilic phase is greater than about 30%, the hydrophilic polymer and drug will exhibit a pore structure 22 that is continuous throughout the volume of the bulk polymer 24, as shown generally at 20 in Figure 2. The continuous pore structure 22 within the bulk polymer volume of the polymer 24 is defined as being above the percolation threshold.

The elution of the drug from a drug release coating, such as is shown in Figure 1, below the percolation threshold, is dependent upon the diffusion of the drug within the drug-enriched polymer 11 through the hydrophobic bulk polymer 12. This is contrary to the diffusion of the drug from a drug release coating above the percolation threshold, such as is illustrated in Figure 2, which is dependent upon the diffusion of the drug from the pore network 22, and upon the mean pore length.

Common solvents and co-solvents usable for the blending of the polymers include dimethyl sulfoxide, N,N-dimethylacetamide, dimethyl sulfoxide-tetrahydrofuran, and isopropanol-water.

Once the polymers are blended and the drug is incorporated in the drug-enriched polymer, the solvent is evaporated. The evaporation is carried out, for some embodiments, at a reduced pressure and at a temperature that is as close to ambient temperature as possible.

Examples of such drugs include antiproliferative substances as well as antineoplastic, anti-inflammatory antiplatelet, anticoagulant, antifibrin,

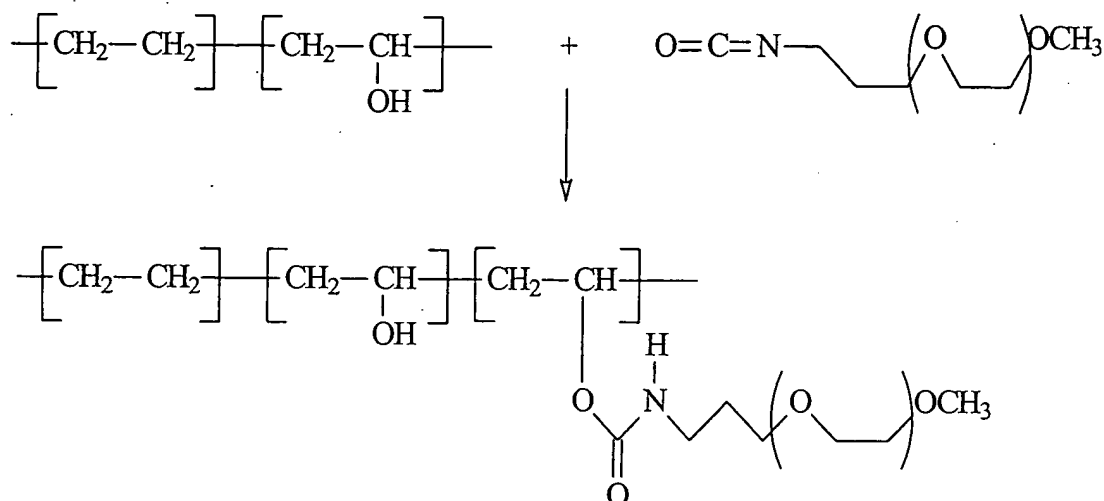
antithrombin, antimitotic, antibiotic, antioxidant, and combinations thereof. A suitable example of an antiproliferative substance includes actinomycin D, or derivatives and analogs thereof, manufactured by Sigma-Aldrich 1001 West Saint Paul Avenue, Milwaukee, WI 53233; or COSMEGEN available from Merck).

- 5 Synonyms of actinomycin D include dactinomycin, actinomycin IV, actinomycin I1, actinomycin X1, and actinomycin C1. Examples of suitable antineoplastics include paclitaxel and docetaxel. Examples of suitable antiplatelets, anticoagulants, antifibrins, and antithrombins, include sodium heparin, low molecular weight heparin, hirudin, argatroban, forskolin, vaspiprost, prostacyclin and prostacyclin
- 10 analogs, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein Iib/IIIa platelet membrane receptor antagonist, recombinant hirudin, thrombin inhibitor, available from Biogen, and 7E-3B, an antiplatelet drug from Centocore. Examples of suitable antimitotic agents include methotrexate, azathioprine, vincristine, vinblastine, antiproliferative agents include
- 15 angiopeptin (a somatostatin analog from Ibsen), angiotensin converting enzyme inhibitors such as CAPTOPRIL, available from Squibb, CILAZAPRIL, available from Hoffman-LaRoche, or LISINOPRIL, available from Merck, calcium channel blockers such as Nifedipine, colchicine, fibroblast growth factor (FGF) antagonists, fish oil, omega 3-fatty acid, histamine antagonists, LOVASTATIN, an inhibitor of
- 20 AMG-CoA reductase, a cholesterol lowering drug from Merck, a cholesterol lowering drug, monoclonal antibodies such as PDGF receptors, nitroprusside, phosphodiesterase, inhibitors, prostaglandin inhibitor, Seramin, a PDGF antagonist, serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine, a PDGF antagonist, and nitric oxide. Other therapeutic substances or agents which may be
- 25 appropriate include alpha-interferon, genetically engineered epithelial cells, and dexamethasone.

In another embodiment, the drug delivery system comprises a polymer film doped with one or more therapeutic drugs. The polymer film is comprised of a graft copolymer, the copolymer having segments that differ

30 significantly in their solubility parameters. The solubility differences result in phase

separation of the two segments. In this embodiment, the hydrophobic polymer is poly(ethylene-co-vinyl alcohol), commercially known as EVAL. In the embodiment, a hydrophilic copolymer such as a polyethylene oxide with a molecular weight between 3200 and 20,000 with an isocyanate functionality is grafted as a side chain, in the following chemical reaction:



The graft copolymer with a molecular weight of 3200 daltons is functionalized with 0.27 mol percent of the hydroxyl functionalities of the poly(ethylene-co-vinyl alcohol) and has an average of two ethylene oxide polymers grafted to the polymer. The total volume fraction of hydrophilic polymer and drug occupies approximately 35% of the polymer matrix and assumes a cylindrical-like pore morphology. The grafted co-polymer with a molecular weight of 3200 daltons functionalized with 0.68 mole percent of the hydroxyl functionalities has an average of five co-polymer segments attached to any given polymer chain. The hydrophilic graft polymer volume containing the polyethylene oxide functionality and the drug, forming a drug enriched polymer, are present at approximately 50 volume percent. The drug enriched polymer assumes a lamellar structure as is shown at 40c in FIG. 3c.

The morphologies of the drug enriched graft polymer 32 within the bulk polymer substrate 34, are shown at 40a, 40b and 40c, respectively, in FIGs. 3a,

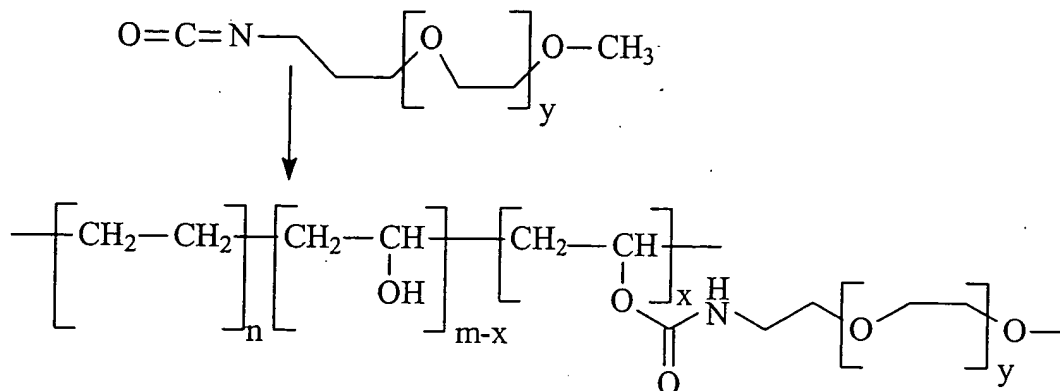
3b and 3c. These different morphologies are due to an increasing concentration of the drug enriched polymer phase 32a, 32b and 32c, respectively, in which one or more drugs is incorporated. At higher concentrations, the drug enriched polymer phase coalesces to form a lamellar morphology. The drug release embodiment 40a, shown in Figure 3a, is a discontinuous pore structure, with the drug-enriched polymer phase 32a discretely dispersed in the bulk phase 34a.

The drug-enriched polymer structure 32b in Figure 3b has a semi-continuous phase and in Figure 3c, the drug-enriched polymer 32c has a continuous phase in which the drug is soluble and diffusible from the continuous phase, when implanted into a living being. The semi-continuous phase 32b comprises sites that are discrete in cross-section but continuous in a longitudinal direction, as is shown in Figure 3b. The continuous phase 32c, shown in Figure 3c, defines a channel 33c in which the drug is diffusible from the bulk polymer 34c to the polymer interface 35. The drug-enriched sites are continuous in both cross-section and in a longitudinal direction.

Example 1

One exemplary composition that produces the drug release morphology of Figure 3c includes an EVAL polymer with 66 weight percent ethylene groups, 43.32 weight percent vinyl alcohol functionalities and 0.68 weight percent vinyl ether groups. The weight percent refers to the percent of the total drug release system weight. The vinyl ether groups were functionalized with PEO-isocyanate, which forms a urethane linkage, using groups that have a molecular weight of a side group of 3200 g/mol. The side groups comprise 33 weight percent of the total EVAL/PEO polymer. The composition of the PEO-isocyanate blend is 75 weight percent functionalized EVAL and 25 weight percent drug. This composition gives rise to a 50 weight percent hard, bulk phase and a 50 weight percent drug/PEO side chain phase. The final structure is a lamellar structure.

The chemical reaction is as follows:



(x) = 66 weight%; (y) = 44 weight%. M is approximately equal to 70 units. Molecular weight is approximately 3200 units. With the drug release system such as is shown at 40c in Figure 3c, drug release is substantially continuous within a human being.

The drug release system of the present invention is deliverable to a treatment site by attachment to a device such as a stent or catheter or guidewire. For other embodiments, the drug release system is encapsulated and ingested or subcutaneously injected. For other embodiments, the drug release system is adhered to a prosthetic device or a graft or other implantable device by methods known to those skilled in the art..

Once positioned within a living being by one of the implantable devices, the drug release system commences delivering drugs because the polymer component of the drug-laden phase is at a temperature below its glass transition temperature. The release of drugs is substantially continuous.

While specified embodiments of the invention have been herein described, it is to be appreciated that various changes, rearrangements and modifications may be made therein without departing from the scope of the invention as defined by the appended claims.